

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NEREUS . 079VP	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/044091	International filing date (day/month/year) 02/12/2005	(Earliest) Priority Date (day/month/year) 03/12/2004
Applicant NEREUS PHARMACEUTICALS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/044091A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/407 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	WO 2004/071382 A (BAYER HEALTHCARE AG; STADLER, MARC; SEIP, STEPHAN; MUELLER, HARTWIG; M) 26 August 2004 (2004-08-26) claim 1 pages 19-20	1-85
Y	WO 2004/043374 A (DANA-FARBER CANCER INSTITUTE, INC.; ANDERSON, KENNETH, C.; HIDEHIMA, TE) 27 May 2004 (2004-05-27) claim 1	1-85
Y	WO 96/32105 A (PRESIDENT AND FELLOWS OF HARVARD COLLEGE; SCHREIBER, STUART, L.; STANDA) 17 October 1996 (1996-10-17) page 2	6, 17, 28, 46, 64, 72-85
	-/-	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document relating to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

13 June 2006

Date of mailing of the international search report

12/07/2006

Name and mailing address of the ISA/
European Patent Office, P.O. Box 5018 Patentkanal 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epi nl,
Fax: (+31-70) 340-3016

Authorized officer

Steendijk, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/044091

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TAUCHI ET AL: "Molecular mechanisms of resistance of leukemia to imatinib mesylate" LEUKEMIA RESEARCH, NEW YORK, NY, US, vol. 28, May 2004 (2004-05), pages 39-45, XP005157790 ISSN: 0145-2126 page 43	59-71
A	ELLIOTT P J ET AL: "The proteasome: A new target for novel drug therapies" AMERICAN JOURNAL OF CLINICAL PATHOLOGY, PHILADELPHIA, PA, US, vol. 116, no. 5, November 2001 (2001-11), pages 637-646, XP008007324 ISSN: 0002-9173 pages 639-641	1-85
P, X, Y	WO 2005/002572 A (NEREUS PHARMACEUTICALS, INC; PALLADINO, MICHAEL; NEUTEBOOM, SASKIA, TH) 13 January 2005 (2005-01-13) claim 6 page 116	1-85
P, X, Y	WILLIAMS P G ET AL: "New cytotoxic salinosporamides from the marine actinomycete Salinispora tropica" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 70, no. 16, 1 July 2005 (2005-07-01), pages 6196-6203, XP002376431 ISSN: 0022-3263 table 3	6, 17, 28, 46, 64, 72-85
E	WO 2006/028525 A (NEREUS PHARMACEUTICALS, INC; POTTS, BARBARA, CHRISTINE; MACHERLA, VENK) 16 March 2006 (2006-03-16) claims	1-85

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/044091

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004071382	A	26-08-2004	AU 2004212296 A1 BR P10407234 A CA 2515940 A1 MX PA05008478 A	26-08-2004 31-01-2006 26-08-2004 18-10-2005
WO 2004043374	A	27-05-2004	AU 2003291356 A1 CA 2504933 A1 EP 1565193 A2 JP 2006509746 T	03-06-2004 27-05-2004 24-08-2005 23-03-2006
WO 9632105	A	17-10-1996	AU 705791 B2 AU 5542396 A CA 2217817 A1 CN 1187769 A EP 0820283 A1 JP 11503732 T NZ 306775 A US 6335358 B1 US 5756764 A US 6147223 A US 6458825 B1 US 6214862 B1 US 6645999 B1 ZA 9602933 A	03-06-1999 30-10-1996 17-10-1996 15-07-1998 28-01-1998 30-03-1999 28-10-1999 01-01-2002 26-05-1998 14-11-2000 01-10-2002 10-04-2001 11-11-2003 03-02-1997
WO 2005002572	A	13-01-2005	AU 2004253478 A1 CA 2532066 A1 EP 1638552 A2	13-01-2005 13-01-2005 29-03-2006
WO 2006028525	A	16-03-2006	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To:

see form PCT/ISA220

Date of mailing
(day/month/year) see form PCT/ISA210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/JS2005/044091

International filing date (day/month/year)
02.12.2005

Priority date (day/month/year)
03.12.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/407 A61P35/00

Applicant
NEREUS PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA220.

3. For further details, see notes to Form PCT/ISA220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4485

Date of completion of
this opinion

see form
PCT/ISA210

Authorized Officer

Steendijk, M

Telephone No. +49 89 2399-8460



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/044091

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/044091

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 12-22,41-85

because:

- ☒ the said international application, or the said claims Nos. 12-22,41-85 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/044091

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-22,28,46,59-85
	No: Claims	23-27,29-45,47-58
Inventive step (IS)	Yes: Claims	
	No: Claims	1-85
Industrial applicability (IA)	Yes: Claims	1-11,23-41
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/044091

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and /or
2. Non-written disclosures (Rules 43bis.1 and 70.9)
see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/044091

- 1) The present application relates to the use of salinosporamides in treatment of drug resistant cancer (claims 1-22), of disease characterized by excessive / inappropriate angiogenesis (claims 23-58), Gleevec resistant cancer (claims 59-72), as well as of specific, alternatively fused salinosporamides for treatment of cancer (claims 72-85, see also claims 6, 17, 28, 46 and 64).
- 2) Cited documents
D1: WO 2004/071382 A
D2: WO 2004/043374 A)
D3: WO 96/32105
D4: LEUKEMIA RESEARCH, vol. 28, (2004-05), pages 39-45
D5: AM. J. CLIN. PATH., .vol. 116, no. 5, (2001-11), pages 637-646
D6: WO 2005/002572 A (2005-01-13)
D7: J.ORG.CHEM., no. 16,(2005-07-01), pages 6196-6203,
D8: WO 2006/028525 A (2006-03-16)

Documents D6-D8 were published after the claimed priority and are herein not considered as prior art.

- 3) Novelty
Document D1 describes various salinosporamides (not the alternatively fused compounds of claims 6, 17, 28, 46, 64 and 72-85) as proteasome inhibitors useful in the treatment of a variety of disorders, including cancer and angiogenic disease (see pages 19-20). This document does not disclose treatment of resistant cancer.
In view of D1 claims 23-27, 29-45, 47-58 are not considered new.

Document D2 describes the use of proteasome inhibitors for treatment of resistant cancer cells, not however specifically of the defined salinosporamides.
Document D3 describes lactacystin analogues useful as proteasome inhibitors; the compounds of D3 lack the substitution "R3" in the compounds presently defined.
Document D4 describes the proposed use of proteasome inhibitors for treatment of Gleevec (imatinib) resistant cancer, not specifically of the defined salinosporamides.
Document D5 describes a variety of applications of proteasome inhibitors, including cancer treatment and as antiangiogenesis agent, however, not specifically of the

defined salinosporamides.

4) Inventive step

In as far as the claimed matter would be new, the following observations as to inventive step apply.

The use of the defined salinosporamides for treatment of resistant cancer cells would seem obvious in the light of D2/D4 in combination with document D1:

As alternative agent for treatment of resistant cancer cells (compare D2/D4) the person skilled in the art would consider other agents which are equally proteasome inhibitors; document D1 describes the defined agents as proteasome inhibitors and would therefore obviously suggest these agents as alternatives to the agents of D2/D4.

The alternatively fused agents of claims 6, 17, 28, 46, 64 and 72-85 had not been described in D1-D5. These derivatives would however seem obvious, active derivatives from the known salinosporamides of D1 in the light of D3, as this document D3 describes for the structurally and functionally closely related lactacystins the possibility of similar, alternative fusion (see meaning of Z2/R1/R2 on i.a. page 2).

5) Further observations

- 5.1 No unifying, common distinguishing aspect with respect to D1 is evident for any particular resistant cancer treatment of known anti-cancer agents and any particular antiangiogenic use of such known agents. Furthermore, no further unifying, common distinguishing aspect of such uses of known agents with the use of the alternatively fused salinosporamides is evident.
- 5.2 The alternatively fused salinosporamides of dependent claims 6, 17, 28, 46 and 64 would not appear to fall under the respective independent claims.
- 5.3 Claims 23 and 41 relate to the use of defined salinosporamides in the treatment of angiogenesis-related disease but continue by specifying that the cancer is leukemia etc. From this definition it is not evident to what type of treatment the claims pertain

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

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(disease characterized by excessive / inappropriate angiogenesis in general or particular cancer types).